AFTER SEVERAL YEARS as coeditor for this journal, I’ve found that coming up with unique ideas for each issue is extraordinarily difficult. This is one of the reasons why I always put my telephone number and e-mail address at the end of this column, thereby facilitating communication with others who just might have an original idea. When all else fails, it becomes time to recycle an older idea—hence, a revisit to the cranial nerves. My predecessor, Ric Harnsberger, covered this subject beautifully during his tenure. Now, several years later, there have been sufficient changes in ideas and equipment to mandate another set of issues on this topic. This issue of Seminars covers cranial nerves I-VI. As you might guess, our June 2002 issue will cover cranial nerves VII-X.

Dr. David M. Yousem, Director of Neuroradiology at Johns Hopkins Hospital, knows more about cranial nerve I than any radiologist I know, so we are very fortunate to have him as the lead author in this issue. Drs. Kader Karli Oguz and Cheng Li also contributed to this state-of-the-art report.

Drs. Michelle M. Smith and James M. Strotmann of the Medical College of Wisconsin collaborated on the next article focusing on cranial nerve II. This contribution includes the entirety of the visual pathways and is a very comprehensive review focusing on visual loss and visual field disturbances. This article is beautifully illustrated and easy to read.

Imaging evaluation of cranial nerves III, IV, and VI are covered exquisitely by Drs. Barbara Eisenkraft and A. Orlando Ortiz from Winthrop-University Hospital on Long Island, New York. This article is also nicely illustrated and easy to read. Dr. Ortiz contributed to our journal previously, and we were very fortunate to be able to coax him into contributing again.

Finally, I had the good fortune of visiting an outstanding scientific exhibit at the RSNA meeting last year which provided detailed information about cranial nerve V authored by Dr. John L. Go of the University of Southern California. I subsequently contacted him regarding his availability to reprise the subject matter for this journal. He and his coauthors, Drs. Paul E. Kim and Chi-Shing Zee, came through with an outstanding contribution.

As is my custom, I encourage feedback on this issue and past issues. More importantly, I am interested in speaking with those of you who have ideas for future issues and topics. Please don’t hesitate to contact me at (610) 526-9942 or e-mail me at swartzjd@aol.com.

Joel D. Swartz, MD
Editor
Imaging of the Olfactory System
David M. Yousem, Kader Karli Oguz, and Cheng Li

The olfactory system consists of the primary olfactory nerves in the nasal cavity, the olfactory bulbs and tracts, and numerous intracranial connections and pathways. Diseases affecting the sense of smell can be located both extracranially and intracranially. Many sinonasal inflammatory and neoplastic processes may affect olfaction. Intracranially congenital, traumatic, and neurodegenerative disorders are usually to blame for olfactory dysfunction. The breadth of diseases that affect the sense of smell is astounding, yet the imaging ramifications have barely been explored.

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THE ANATOMY AND PHYSIOLOGY of olfaction have rarely been the subject of articles in the radiologic literature, in part because this special sense is the least appreciated one in the neurosciences. All too often the olfactory system is ignored in the usual clinical evaluation of a patient, hence, the common recording that “cranial nerves II to XII are intact.” Nonetheless, to the astute clinician and conscientious neuroradiologist, knowledge of the ramifications of olfactory dysfunction is very rewarding. Therefore, this article initially focuses on the functional anatomy of the sense of smell and then addresses those protean entities that affect cranial nerve I (see Table 1). Both peripheral and central diseases that impact on the sense of smell are explored.

ANATOMIC IMAGING (NORMAL)

Smells are perceived in the upper nasal cavity by olfactory neuroepithelial receptors. The primary olfactory nerves pierce the cribriform plate to stimulate and synapse with olfactory bulb nuclei. In truth, the true olfactory nerves are located in the nasal cavity and these should be termed cranial nerves I (CN I). Instead, the olfactory bulb and tract, which is a secondary neuron, is usually referred to as the first cranial nerve (Fig 1). From the olfactory bulb, fibers travel in the olfactory tract to enter the brain just lateral and anterior to the optic chiasm. Fibers continue into medial and lateral olfactory striae to septal nuclei at the base of the brain just inferior and anterior to the rostrum of the corpus callosum. Axons from mitral and tufted cells project to central brain limbic system components including the pyriform and entorhinal cortex and adjacent corticomedial amygdala (which together form the uncus), the ventral striatum, the parahippocampus area, and the anterior olfactory nuclei. From these areas there are widespread interconnections with many parts of the brain, including the mediodorsal thalamus, hypothalamus, orbitofrontal and dorsolateral frontal cortex, temporal cortex, and other areas of the limbic system (Fig 2).

The sizes of the olfactory bulbs and tracts (OBTs) have recently been reported in the literature.1 The left and right OBT volumes peak in the fourth decade of life, but show considerable variation within each subject group (see Table 2).

The mean left and right OBT volumes and the mean combined volume show a decline in the seventh and eighth decade that parallels a decline in scores by the patients on the University of Pennsylvania Smell Identification Test (UPSIT) scores. Thus, as the volume declines, function declines. A Kruskal-Wallis test, performed to detect differences between the means of OBT volumes between decades showed borderline significance at P = .05 for the left OBT, but not the right. The biggest differences noted were between the fourth and seventh decade for right and left OBTs. By using regression analysis based on the generalized estimating equations model,2 OBT volumes show significant decreases between decades of life (P = .027).

As measured in large population studies by using the UPSIT, there is an initial increase in odor identification capability to the third decade of life, at which time the UPSIT scores plateau.3 At about

456 Seminars in Ultrasound, CT, and MRI, Vol 22, No 6 (December), 2001: pp 456-472
Table 1. Causes of Olfactory Dysfunction

<table>
<thead>
<tr>
<th>Conductive Disorders</th>
<th>Primary Olfactory Apparatus Lesions</th>
<th>Neurodegenerative Disorders</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>Sinusitis</td>
<td>Alzheimer’s disease</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Polyposis</td>
<td>Traumatic injury</td>
<td>Parkinson’s disease</td>
<td>Infection</td>
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<td>Sinonasal cavity neoplasms</td>
<td>Congenital aplasia, hypoplasia</td>
<td>Huntington’s disease</td>
<td>Surgery</td>
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<td>Olfactory neuroblastoma</td>
<td>Schizophrenia</td>
<td></td>
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<td></td>
<td>Cocaine</td>
<td>Multiple sclerosis</td>
<td></td>
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<tr>
<td></td>
<td>Toxins</td>
<td>Temporal lobe epilepsy</td>
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<td>Viral infections</td>
<td>Korsakoff’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
</tr>
</tbody>
</table>

age 60, however, a decline in median UPSIT scores begins to be seen across patients to the point that nearly 75% of individuals over 80 years old score 19 or less on the 40-item UPSIT test. These patients are severely hyposmic or anosmic. Similar changes in odor threshold values for phenyl ethyl alcohol are noted, however, the drop-off starts to be seen at about age 40 in men and 60 in women. Smokers and men tend to have higher thresholds than nonsmokers and women, respectively. A change in the perception of pleasantness of taste also occurs with age. This effect can be eliminated when the nostrils are occluded and the olfactory influence on taste is nullified.

Several theories have been espoused as to why the sense of smell declines with age and include: (1) reduction in volume of the sensory neuroepithelium caused by cumulative effects of viral infections, (2) replacement of the olfactory neuroepithelium with nonsensory columnar epithelium in the olfactory clefts of the nose, (3) diminution in central neurotransmitters (eg, norepinephrine), (4) reduction in patency of the airway, (5) variations in the nasal cycle with age, or (6) reduction in resistance of the olfactory neuroepithelium to infectious or toxic insults.

The finding of a decline in the human OBT volume with advancing age lends credence to the idea of a reduced amount of afferent input to the olfactory bulbs and tracts from the olfactory neuroepithelium and ciliated nerves that pierce the cribriform plate. A decrease in central neurotransmitters is a less plausible explanation for the quantitative findings because the predominant effect seen is at the bulb and tract level, not at the cortical level.

FUNCTIONAL IMAGING (NORMAL)

Functional magnetic resonance imaging (fMRI) has been used in an attempt to localize regions of the brain associated with olfaction. Koizuka et al have noted bilateral increased cerebral blood flow in the inferior frontal lobes, piriform cortex, and orbitofrontal regions after phenyl ethyl alcohol olfactory stimulation. Wexler et al showed similar areas of activation in these and other limbic structures when odors were presented to normal volunteers.

Yousem et al have performed olfactory-stimulated functional magnetic resonance imaging (OSfMRI) in 18 normal subjects between 29 and 43 years of age by using a homemade olfactometer in which odors from 3 sources were alternated at 5-second intervals for 30 seconds during the on stimulus and room air was used for 30 seconds for the off stimulus. They found that odors that stimulated only CN I had extensive activation that was localized to the orbitofrontal region (Brodman area 11) and the cerebellum. The volume of activation was greater in the right orbitofrontal region than the left (Table 3, Fig 3).

Some odorants not only stimulate the olfactory system but also activate trigeminal neurons that abound in the nasal cavity. Stimulants such as carbon dioxide that “sting or burn the nose” tend to have more fifth-cranial nerve input. When Yousem et al applied an fMRI paradigm with odorants that also induce trigeminal nerve stimulation they found wider activation of many different areas, including visual and cingulate areas (Table 4, Fig 4). Yousem et al found that there was accommodation (diminution of brain activation) to pleasant olfactory nerve-mediated odors, but amplification (an increase in brain activation) to repeated testing with trigeminally mediated odors.

Fulbright et al reported that pleasant odors lateralized to the left insula region whereas the unpleasant odors were more left frontal.

In a study of the effects of age on fMRI, older right-handed patients (mean age 73.2 years)
and 5 younger right-handed patients (mean age of 23.8 years) underwent blood oxygenation level dependent (BOLD) fMRI scans that used binasal olfactory nerve stimulation. The data were normalized to a standard atlas, and individual and group statistical parametric maps (SPMs) were generated for each task. The SPMs ($P < .01$) of volumes of activation and distribution of cluster maxima were
Fig 2. Connections to cortex from the olfactory system (diagram or graph). Organization of the human olfactory system. (A) Peripheral and central components of the olfactory pathway. (B) Enlargement of region boxed in (A) showing the relationship between the olfactory epithelium, containing the olfactory receptor neurons, and the olfactory bulb (the central target of olfactory receptor neurons). (C) Diagram of the basic pathways for processing olfactory information. (D) Central components of the olfactory system. (Reprinted with permission.)

<table>
<thead>
<tr>
<th>Decade</th>
<th>Mean LOBT Volume (μL)</th>
<th>Standard Deviation</th>
<th>Mean ROBT Volume (μL)</th>
<th>Standard Deviation</th>
<th>Mean OBT Volume (μL)</th>
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</thead>
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<tr>
<td>3rd</td>
<td>122.7</td>
<td>17.1</td>
<td>129.1</td>
<td>9.8</td>
<td>125.9</td>
</tr>
<tr>
<td>4th</td>
<td>158.7</td>
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<td>41.7</td>
<td>131.6</td>
<td>29.9</td>
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<td>26.8</td>
<td>129.3</td>
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<tr>
<td>7th</td>
<td>108.5</td>
<td>29.4</td>
<td>123.9</td>
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<td>114.5</td>
<td>31.0</td>
<td>124.7</td>
<td>15.0</td>
<td>119.6</td>
</tr>
</tbody>
</table>

Abbreviations: R, right; L, left.
Reprinted with permission from Yousem et al.
compared for the 2 patient groups. Analysis of the group SPMs revealed activation in the frontal lobes, perisylvian regions, and cingulate gyri. More voxels were activated in the younger group than the older group (Fig 5). The right inferior frontal, right perisylvian, and right and left cingulum had the largest number of voxels activated. The most common sites of activation on individual maps in both groups were the right inferior frontal regions and the right and left superior frontal and perisylvian zones. Young patients activated these regions more frequently than older patients and the younger patients activated more voxels (Table 5).

On standardized tests of odor identification and odor detection in nearly all age groups, women score better than men. Yousem et al studied whether these findings would translate to differences between the sexes in the volume of activated brain with odor-stimulated fMRI. The activation maps of 8 right-handed women (mean age 25.3 years, range 20–44 years, standard deviation 6.5 years) given the same olfactory stimuli in an fMRI experiment at 1.5 T.

The women’s group averaged activation maps showed up to 8 times more activated voxels than did those of men for specific regions of the brain (Table 6, Fig 6). In all sites, women showed more activated voxels than men. The difference was most striking in the right temporal (peri-insular) regions. When individual patients were studied, Yousem et al found that all women and 7 of 8 men showed some degree of activation, but that the sites of activation varied widely. Six of 8 men activated the right superior frontal region and the right perisylvian region. Half of the men activated the left perisylvian and right inferomedial temporal zone. All other sites showed activated voxels in fewer than half of the men.

**Table 3. Pleasant Olfactory Nerve fMRI Stimulation Values**

<table>
<thead>
<tr>
<th>Size of Activation (FPQ* Units)</th>
<th>FPQ Value</th>
<th>Brodmann Area No.</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>43, 16</td>
<td>2.5, 2.1</td>
<td>11</td>
<td>Right orbitofrontal</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>11</td>
<td>Left orbitofrontal</td>
</tr>
<tr>
<td>10</td>
<td>2.1</td>
<td>Not provided</td>
<td>Cerebellum</td>
</tr>
</tbody>
</table>

*FPQ over 2.0 considered statistically significant.

**Table 4. Trigeminal Odor fMRI Stimulation Values**

<table>
<thead>
<tr>
<th>Size of Activation (FPQ* Units)</th>
<th>FPQ Value</th>
<th>Brodmann Area No.</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>2.5</td>
<td>19</td>
<td>Left primary visual cortex</td>
</tr>
<tr>
<td>58</td>
<td>2.2</td>
<td>30</td>
<td>Retrosplenial cortex</td>
</tr>
<tr>
<td>53</td>
<td>2.8</td>
<td>19</td>
<td>Right primary visual cortex</td>
</tr>
<tr>
<td>49</td>
<td>2.1</td>
<td>23</td>
<td>Posterior cingulate</td>
</tr>
<tr>
<td>24</td>
<td>2.5</td>
<td>6</td>
<td>Premotor and SMA</td>
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<tr>
<td>22</td>
<td>2.1</td>
<td>7</td>
<td>Precuneus</td>
</tr>
<tr>
<td>22</td>
<td>2.1</td>
<td>Not provided</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>21</td>
<td>2.2</td>
<td>11</td>
<td>Orbitofrontal cortex</td>
</tr>
</tbody>
</table>

*FPQs over 2.0 considered statistically significant.

*Fig 3. Orbitofrontal activation with fMRI. Note the perisylvian (curved arrow) and orbitofrontal (straight arrow) activation of the brain in this group map of patients who were presented with a combination of hydrogen sulfide and rose oil (phenylethyl alcohol), pure olfactory nerve stimulants. Right more than left activation is seen.*
Fig 4. Trigeminal stimulation with fMRI. With carbon dioxide, a trigeminal nerve stimulant, periclingulate, perisylvian (curved arrow, black arrow), inferior frontal (straight arrows), and brain stem activation becomes more apparent.

Fig 5. Results of fMRI of young patients compared with older patients. (A) Young patients show greater perisylvian and frontal activation (arrows), given a cranial nerve I stimulant, than (B) older subjects.
Table 5. Olfactory fMRI Data: Young Versus Old

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Left Frontal Voxels Activated</th>
<th>Right Frontal Voxels Activated</th>
<th>Left Temporal Voxels Activated</th>
<th>Right Temporal Voxels Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Old</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: R, right; L, left; I, inferior; S, superior; F, frontal; M, medial; T, temporal; P, perisylvian; C, cingulate.

DISEASE STATES (PERIPHERAL)

Sinonasal Inflammatory Disease

Sinonasal tract disease is one of the common causes of olfactory disturbance. The cause of the olfactory deficits among patients with nasal and paranasal sinus disease is most likely caused by nasal airway obstruction. Recently, the influence of nasal obstruction on olfaction has been comprehensively reviewed. Any cause of bilateral obstruction can lead to decreased smell sensations by limiting airflow to the olfactory receptors. Besides the obstructive effect, lesions that are located in the upper nasal vault and/or cribriform plate region may also directly damage the olfactory epithelium and olfactory neurons.

Paranasal sinusitis (Fig 7) is a relatively common disorder affecting approximately 30% of the population at some time in their lives. One of the common symptoms of acute and chronic paranasal sinusitis is decreased smell sensation, which is generally reversible. The prompt diagnosis and treatment of sinusitis are important for restoring olfactory function. Though the exact cause of chemosensory dysfunction secondary to sinusitis is elusive, alterations in nasal air flow and mucociliary clearance or obstruction from secretory products, polyps, or retention cysts may contribute to olfactory dysfunction. At present, high-resolution computed tomography (CT) is the preferred imaging technique to evaluate for sinusitis, preceded by nasal endoscopic examination. CT helps the functional endoscopic sinus surgeons in planning effective surgery to restore olfactory ability and normal mucociliary clearance.

Allergic Reaction

Allergic rhinitis is a common upper-airway condition affecting about 30 million Americans with peak prevalence in the age group from 35 to 54 years. Hyposmia or anosmia is common with allergic rhinitis, mainly caused by nasal obstruction by polyps or inflamed mucosa, which limit access of inspired air to the roof of the nasal vault. The diagnostic work-up begins with a careful history that attempts to identify offending allergens. Skin testing of specific antigens is often used to confirm the diagnosis. Medical imaging studies play a supplementary role in the evaluation of sinonasal airway status and differential diagnosis. CT and MRI are also important for detecting any complications such as sinusitis, mucoceles, and aggressive polyps in patients with allergic rhinitis. Rounded excrescences and enlargement of ostia are seen in the airway of patients with polyposis.

Trauma

The incidence of posttraumatic anosmia ranges from 24% to 30% for severe head injuries, 15% to 19% for moderate head injuries, and 0% to 16% for mild head injuries. Blows to the frontal region or the occiput are commonly associated with posttraumatic anosmia. Sumner found that a blow to the occiput has 5 times the chance of inducing anosmia than a blow to the forehead if posttraumatic amnesia is present (indicating a severe head injury).
Fig 6. Women versus men fMRI results. (A) Women show more activation than (B) men, especially in the perisylvian regions and frontal (arrows). Note right-sided dominance.

Injury). This may be caused by contra coup shearing effects at the cribriform plate and inferior frontal lobe region. Side impact injuries also can cause olfactory dysfunction at a high rate. Nonetheless, because frontal injuries are more common than occipital or lateral blows, posttraumatic anosmia is most often seen in the setting of a frontal contact injury. Fractures of the skull or face are seen in 45% to 68% of individuals with bilateral posttraumatic anosmia.

Of 268 patients with head trauma who presented to the University of Pennsylvania Smell and Taste Center evaluated by Doty et al, 66.8% had anosmia, 20.5% had microsmia, 15.4% had persistent parosmia, and 12.7% had normosmia. On retesting, less than 2% recovered olfactory function.

Fig 7. Sinusitis/polyps. Complete opacification of the upper nasal cavity, maxillary antra, and ethmoid sinuses is seen in this patient with sinonasal polyposis and postobstructive sinusitis. Depending on the chronicity of the disease, the patient may sustain permanent smell loss.
completely, 36% improved slightly, 45% had no change, and 18% worsened.

Retention of the sense of smell in one nostril is uncommon (<11% of patients) in posttraumatic patients evaluated for chemosensory abnormalities. In patients who have partial or incomplete loss of olfactory function, the deficit may go completely unnoticed.

Recovery of olfactory function after head trauma is variable. Return of olfactory function can occur in 14% to 39% of patients initially anosmic, especially if the interval of posttraumatic amnesia is less than 24 hours. Although 74% of patients recovering olfactory function do so within 12 weeks, 1 study reported that an additional 22% will regain function by the second year after the injury. Despite the fact that reports of return of olfactory function as long as 7 years after injury have been published, few studies have used quantitative tests of olfactory function. Olfactory neurons have the capacity for neurogenesis allowing new receptor growth, so it is surmised that the late return of function may be related to a peripheral (olfactory nerves-bulbs-tracts) mechanism rather than a more central one. In humans it is believed that there may be fibrotic scarring that occurs at the cribriform plate that may prevent regenerating axons from connecting to the secondary neurons of the olfactory bulb.

To evaluate the sites of injury in patients with posttraumatic olfactory deficits, Yousem et al studied 25 patients with posttraumatic smell dysfunction by using olfactory testing and MR. Quantitative and qualitative gradings for olfactory bulb, tract, subfrontal region, hippocampus, and temporal lobe damage were correlated with olfactory test results. Twelve patients were anosmic, 8 had severe impairment, and 5 were mildly impaired. Olfactory bulb and tract (88% of patients), subfrontal (60%), and temporal lobe (32%) injuries were found (Fig 8), but did not correlate well with the UPSIT scores. Odor discrimination deficits correlated best with frontal injury and odor memory correlated best with temporal lobe damage. These relationships did not achieve statistical significance. The finding that the OBT volumes in patients with posttraumatic anosmia are smaller than those of patients with residual smell function or control subjects suggests that the source of the olfactory deficit after trauma may be at the OBT.
level or even more proximally in the olfactory neurons. Shearing of nerves at the cribriform plate is the most plausible explanation.

CONGENITAL

Congenital anosmia is said to exist when a patient has no recall of smell sensation dating to early childhood. Some patients report a reduced sense of smell since birth (congenital hyposmia) and still others who claim to have no sense of smell may show some residual or normal function on laboratory testing. Although the etiology of early anosmia or hyposmia may include such entities as viral infections, posttraumatic injury to the olfactory epithelium, choanal atresia, holoprosencephaly, septo-optic dysplasia, meningoencephaloceles that affect the frontoethmoidal region, or Kallmann’s syndrome (anosmia with hypogonadotropic hypogonadism), studies conducted by Jafek et al and Leopold et al suggest that congenital anosmia usually does not occur in association with other anomalies.

Kallmann’s syndrome was extensively described in 1944 and has been the focus of a number of clinical, genetic, and pathologic studies. The disorder appears to be found most commonly as an x-linked disorder, but can be inherited through autosomal transmission as well. Patients are eunuchoid and may have coexistent renal anomalies, cleft lips or palates, infertility, spastic paraplegia, cerebellar dysfunction, nystagmus, or hearing loss. Although most initial reports noted the absence of olfactory bulbs and tracts in Kallmann’s syndrome macroscopically, the presence or absence of olfactory neuroepithelium in patients with congenital anosmia and/or Kallmann’s syndrome is still being debated. Thus, 2 camps have developed; those that believe that Kallmann’s syndrome patients have no epithelium and those that believe that the olfactory axons simply fail to reach the prosencephalon and hence do not connect intracranially. The hypogonadism of Kallmann’s syndrome is thought to be caused by either a lack of cells that can express luteinizing hormone releasing hormone (LHRH) or by abnormal migration of the LHRH neurons from the olfactory placode in the nose to the hypothalamus. Truwit et al support the neuronal migrational anomaly theory. They believe that soft tissue seen by MR in the region below the expected location of the olfactory bulbs represents arrested neurons.

In a study of 24 individuals with congenital anosmia, Yousem et al showed absence of the olfactory bulbs and tracts in 16 patients, hypoplasia of bulbs and tracts in 4 patients, and absent bulbs but hypoplastic tracts in 4 patients (Fig 9). Three individuals could smell, though with severe deficits (UPSITS 18–24 of a possible 40), and 2 of the 3 had intact small bulbs and tracts. Yogl et al also documented the ability of MR to show abnormalities of the olfactory pathway in patients with congenital anosmia. Eighteen patients diagnosed with Kallmann’s syndrome and 10 patients with idiopathic hypogonadotrophic hypogonadism were included in this study, which used a head coil. Seventeen of the 18 patients with Kallmann’s syndrome showed absence of the olfactory bulbs and tracts and 8 of these individuals had normal olfactory sulci adjacent to the gyrus rectus. Olfactory

Fig 9. Congenital anosmia. (A) No olfactory bulbs or tracts can be seen in this individual with congenital anosmia. Note also the absence of well-formed olfactory sulci (compare with Fig 1). (B) The same findings are seen in this patient who has never smelled the scent of a flower.
bulbs and tracts were present in all 10 patients who had idiopathic hypogonadotropic hypogonadism, though 3 showed some degree of hypoplasia. In 3 other studies of patients with Kallmann’s syndrome, complete absence or hypoplasia of the olfactory bulbs and tracts was the predominant finding. The olfactory sulci may be variably aplastic, hypoplastic, or normal.

TUMORS OF THE NASAL CAVITY AND PARANASAL SINUSES

Neoplasms of the sinonasal tract are uncommon. Malignant tumors of the nasal cavity and paranasal sinuses account for only 0.2% to 0.8% of all human malignancies. Early symptoms of sinonasal tract tumors, nasal discharge, unilateral nasal obstruction, and minor intermittent epistaxis may simulate low-grade chronic infection. Almost all sinonasal tract tumors and tumor-like conditions that grow to a large size may cause a decline in olfactory acuity by interfering with patency of the nasal airway or directly destroying the olfactory receptors. The most common malignancies of the sinonasal system are squamous cell carcinoma and adenocarcinoma, but lymphoma, melanoma, adenoid cystic carcinoma, and chondrosarcomas also populate the nasal cavity. Two examples of intrinsic sinonasal tract tumors relatively unique to the sinuses (the olfactory neuroblastoma and the inverted papilloma, both of which often cause hyposmia or anosmia) may serve as prototypes for masses in this region.

OLFACTORY NEUROBLASTOMA

Olfactory neuroblastoma, or esthesioneuroblastoma, is a rare nasal tumor originating from the olfactory neuroepithelium lining the roof of the nasal vault and in close proximity to the cribiform plate. There have been less than 300 reported cases in literature worldwide. Olfactory neuroblastomas occur in all age groups with a peak incidence in the 11 to 20 and 51 to 60 years age groups. There is a slight preponderance of the tumor in women. The incidence of olfactory neuroblastoma has been estimated to range from 2% to 3% of all malignant intranasal neoplasms. The most common symptoms are unilateral nasal obstruction and recurrent epistaxis. Hyposmia and rhinorrhea are not unusual. Extension into the orbit, paranasal sinuses, or anterior cranial fossa may cause vision disturbances and headache. In the detection and staging of olfactory neuroblastoma, CT and/or MRI play an important role. Generally speaking, MRI is more accurate than CT in showing the tumor’s intracranial extent. MRI is also exquisitely useful for differentiating neoplasm from postobstructive secretions because of the difference in the signal intensity (secretions are bright on T2, tumor intermediate) and gadolinium enhancement. Unfortunately, signal intensity characteristics of various sinonasal tract tumors overlap each other, so MRI cannot usually predict specific tumor histology. However, a recently described imaging finding characteristic of olfactory neuroblastomas is the presence of peripheral peritumoral cysts along the intracranial portion of the tumor. If stippled calcifications are also seen on CT, the diagnosis is relatively assured.

INVERTED PAPILLOMA

The inverted papilloma is a relatively rare and locally aggressive sinonasal tumor. It constitutes 0.5% to 4% of primary nasal tumors and occurs in all age groups and in men more than women. The most common presenting symptoms are nasal obstruction, epistaxis, and hyposmia. Subsequent sinusitis and tumor extension into the sinuses and orbits can cause purulent nasal discharge, pain, and diplopia. Radiographic findings of inverted papilloma can vary from a small nasal polypoid nodule to an expansile large mass, which may remodel the nasal vault and extend into the sinuses, orbits, or even the anterior skull base. CT and MRI are very useful in defining the location and extension of the tumor. Yousem et al have shown that this tumor can be separated from obstructed secretions based on lower T2-weighted (T2W) signal intensity and solid enhancement in inverted papillomas. However squamous cell carcinoma and inverted papillomas look alike (Fig 10), which is important because coincidental carcinomas occur in up to 15% of patients with inverted papillomas.

Other benign neoplasms to affect the sinonasal cavity include osteomas, enchondromas, schwannomas, and juvenile angiofibromas.

Malignant Neoplasms

Squamous cell carcinomas account for 80% of the malignancies that affect the paranasal sinuses and 80% occur in the maxillary sinus. The hallmark of malignancies of the sinonasal cavity is bony destruction, which is seen in approximately 80% of CT scans of sinonasal squamous cell carcinoma at initial presentation. The lesion is
IMAGING OF THE OLFATORY SYSTEM

Fig 10. Inverted papilloma. Separating the low-intensity inverted papilloma (*) from the high-intensity secretions (S) is easy on the T2-weighted scan in this patient.

...confined to the maxillary antrum in only 25% of cases at presentation. In most series, the lesion is characterized by a low-signal intensity on T2W scans. This is why differentiation with obstructed secretions that are typically bright in signal intensity on T2W scans is so easy on MRI.

Minor salivary gland tumors and melanoma are the next most common malignancies to affect the sinonasal cavity after squamous cell carcinoma. The minor salivary gland tumors represent a wide variety of histologic types including adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and sinonasal undifferentiated carcinoma. Of all minor salivary gland tumors, adenoid cystic carcinoma is the most common variety. Its signal intensity may be high or low on T2W scans, possibly related to the degree of tubular or cribriform histologic pattern as well as cystic spaces, necrosis, and tumor cell density. Tissue specificity is not readily achievable with MRI or CT. Gadolinium is of particular use with adenoid cystic carcinomas, which have propensity for perineural spread. Enhancing cranial nerves may be present. With sinonasal cavity malignancies one should always attempt to trace back the branches of the fifth cranial nerve via the pterygopalatine fossa, foramen rotundum, foramen ovale, and orbital fissures to identify perineural neoplastic spread.

Adenocarcinomas of the paranasal sinuses have a predilection for the ethmoid sinuses and appear more commonly in woodworkers. This tumor also tends to have low-signal intensity on T2W MRI images, but may have high-signal intensity in a small percentage of patients.

Sarcomas of the sinonasal cavities are very rare, with chondrosarcoma the most common. Again, the histologic diagnosis is probably better suggested by CT based on the characteristic whorls of calcification. However, for staging, MRI is competitive with CT and, particularly if repeat examinations are going to be required, follow-up with MRI to avoid the radiation exposure of CT is recommended.

Melanoma is a tumor that is usually identified in the nasal cavity as opposed to the paranasal sinuses. It has been associated with melanosis in which there is field deposition of melanin along the mucosal surface of the sinonasal cavity. Therefore, multiplicity of lesions becomes a problem when dealing with melanomas. Neither CT nor MRI is particularly helpful in identifying the microscopic field cancerization of melanoma. When melanoma contains melanin there is paramagnetism that causes T1 and T2 shortening (Fig 11), accounting for high-signal intensity on T1W scans and low-signal intensity on T2W scans. However, an amelanotic melanoma may have bright signal intensity on T2W scans. The presence of hemorrhage associated with the melanoma, a common occurrence because of the coincidence of epistaxis, may further obfuscate the signal intensity pattern.

Lymphoma does occur in the paranasal sinuses and may have variable signal intensity as well. It is characterized by homogeneous signal intensity without necrosis and is associated with cervical lymphadenopathy.

Metastatic disease to the paranasal sinuses is extremely rare. Of the primary causes of metastases to the sinuses, renal cell carcinoma is probably the most common. This is a tumor that also has a propensity for hemorrhage and that may also have a variable signal intensity depending on the stage of hemorrhage.

MISCELLANEOUS PERIPHERAL CAUSES

It is estimated that 30 million Americans have used cocaine and 5 million use it regularly. Intranasal use of cocaine and heroin has reached epidemic proportions in the United States. Although hyposmia or anosmia has been suggested to occur often in cocaine abusers, few studies that used quantitative measures of olfactory function have confirmed such reports. A recent study reported that, of 11 cocaine abusers who underwent detailed olfactory testing, only 1 was found to be anosmic and another had mild olfactory discrimi-
nation dysfunction. These investigators note that most cocaine abusers do not develop permanent olfactory dysfunction. If, in fact, olfactory disturbance occurs as a result of heavy cocaine use, it could be caused by associated conductive disorders, nasal airway obstruction, alteration in sinonasal aerodynamics, damage to the olfactory epithelium, damage to the central olfactory system, or osteolysis of the cribriform plate.

Within the differential diagnosis for nasal septum cartilaginous destruction, one should include Wegener’s granulomatosis, syphilis, leprosy, lymphoma, rhinoscleroma (a klebsiella infection), and fungal invasion.

Hyposmia or anosmia induced by occupational or accidental exposure to toxins has been traditionally thought to be caused by damage to the peripheral pathways. However, one study has suggested that olfactory deficits caused by occupational exposure to toxins (acrylates or methylacrylates) have both peripheral toxic and central nervous system (CNS) effects. One report of anosmia as a sequela of hydrogen sulfide (H2S) inhalation suggested the loss to be caused by central brain damage.

DISEASE STATES (CENTRAL)

Neurodegenerative Disorders

Dementia of the Alzheimer’s type. From a clinical perspective, one of the earliest manifestations of dementia of the Alzheimer’s type (DAT) is a loss of odor perception. This is accounted for pathologically by the presence of neurofibrillary tangles, neuritic plaques, and cholinergic neuronal loss in olfactory eloquent regions of the brain: the entorhinal cortex, the olfactory bulbs, the hippocampi, the olfactory nuclei, and the piriform cortex (Fig 12). It appears that the olfactory system is damaged early in DAT, with spread of neurofibrillary tangles from the entorhinal cortex to the limbic system, then to neocortical areas. Primary
olfactory cortices are involved in more advanced stages of the disease. A theory espousing the possibility that DAT is a transmissible disease spread through the nasal passages has emphasized the early involvement of the olfactory system with DAT. The investigators note that (1) neurofibrillary tangles are seen in olfactory eloquent areas including the bulbs, (2) olfactory dysfunction is invariably seen in patients with DAT, (3) olfactory deficits are present early in the disease, predating cognitive decline, (4) patients may be unaware of deficits, (5) the olfactory deficits appear to be unrelated to cognitive deficits both anatomically and functionally, (6) the olfactory dysfunction mimics that in Parkinson’s disease and Huntington’s disease, and (7) DAT progression can be followed through olfactory testing. Nonetheless, the volumes of the OBTs in DAT have not been shown to be reduced in a preliminary study comparing OBT volume and age-matched controls. Clearly, however, temporal lobe volume loss is apparent in DAT.

Multiple sclerosis. Multiple sclerosis (MS) affects millions of Americans in the prime of their lives. Though the influence of MS on the sense of smell has long been controversial, recent MRI studies have showed that the olfactory function in patients with MS has closely correlated with the load of demyelinating plaques within central olfactory processing areas of the brain. In 1997, Doty et al. found a strong negative relationship (Spearman r = −.94) between the UPSIT scores and the number of MRI-determined plaques within the inferior frontal and temporal lobe regions of the brain. Another study has also shown a close association, longitudinally, between the remission and exacerbation of plaque numbers and UPSIT scores, with more plaques in the brain olfactory processing areas reflecting lower UPSIT scores.

Parkinson’s disease. Odor detection and identification are significantly impaired in patients with Parkinson’s disease (PD). Research into the cause of smell dysfunction in patients with PD has focused on dopaminergic changes. Patients with PD show significantly reduced mean uptake of F-dopa in the caudate nuclei and putamen, a reduction of striatal dopamine storage, and reduced activity in basal ganglia. However, the olfactory deficit is unrelated to the severity of motor or cognitive symptoms, and is not improved by L-dopa therapy. Olfaction in parkinsonism-dementia complex (PDC) of Guam is similarly affected, but in patients with progressive supranuclear palsy and patients with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism, olfactory function is normal. This may be a differential point.

Acquired immune deficiency syndrome. Olfactory deficits of patients with human immunodeficiency virus (HIV) infection have been recently reported. Patients with acquired immune deficiency syndrome (AIDS) dementia score lower on UPSIT tests than those who have clinical disease without dementia who, in turn, score worse than those who are seropositive without disease who still perform worse than normal controls. Everall et al. have found that the neuronal numeric density in the frontal cortex is significantly lower in the HIV group than in a control group, with a loss of about 38% of neurons in the superior frontal gyrus. This may account for the olfactory deficits in these patients. Patients with AIDS also develop sinusitis more frequently.

A number of other neurodegenerative disorders including Huntington’s disease, Korsakoff’s psychosis, and multisystem atrophy show significant olfactory function loss during the course of the diseases. Schizophrenia. Impaired olfactory function has been reported in schizophrenic patients, especially men. These olfactory deficits, which are not of the same magnitude as those seen in patients with AD and PD, are perhaps not unexpected, given the occurrence of olfactory hallucinations as symptoms in a number of patients with schizophrenia.
nia, and the evidence linking both to temporal lobe dysfunction. Kopala et al\textsuperscript{85} studied olfactory identification ability in pre- and postmenopausal patients with schizophrenia as well as control subjects. Olfactory deficits were present in all schizophrenic patients, but at a more pronounced level in postmenopausal ones. The investigators stated that estrogen deficiency aggravates the condition originating from schizophrenia.

Neuropathologic studies in schizophrenic patients have reported neuronal loss in the entorhinal region and prefrontal cortex, gliosis in the basal limbic structures of the forebrain, and atrophy in temporolimbic structures. Neuropsychiologic studies (including regional cerebral blood flow, brain electrical activity mapping, and regional metabolic activity in the brain) in patients with schizophrenia have shown prefrontal cortex and temporal lobe dysfunction.\textsuperscript{87} Functional imaging, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), has provided some evidence that certain schizophrenic patients have decreased blood flow and metabolism in the frontal lobes (hypofrontality).

Anatomic imaging findings have basically paralleled the neuropathologic changes in the brains of patients with schizophrenia. The most consistent finding (on both CT and MRI) is an increase in the size of the cerebral ventricular system, especially in the frontal and temporal horns, and corresponding decreases in cerebral tissue, especially in the prefrontal cortex and in medial temporolimbic structures.\textsuperscript{87} Suddath et al\textsuperscript{88} evaluated the volume of the temporal lobes in patients with schizophrenia by a quantitative MRI study. The results showed that the volume of temporal lobe gray matter was 20\% smaller in the patients than in the control subjects and lateral ventricular volume was 67\% larger in the schizophrenia group than in the control group. Schizophrenic patients tend to have smaller hippocampi than matched controls. In a recent volumetric MRI study by Turetsky et al,\textsuperscript{79} patients with schizophrenia exhibited 23\% smaller olfactory bulb volumes bilaterally than comparison subjects.

Epilepsy. Kohler et al\textsuperscript{89} studied patients with schizophrenia and right and left mesial temporal lobe epilepsy (TLE). Patients with schizophrenia and right-sided TLE exhibited significant impairment on olfactory tests, whereas patients with left-sided TLE and controls performed comparably. This study corroborates the right-sided dominance of olfaction.\textsuperscript{89} Unpleasant olfactory auras associated with seizures are not uncommon, and epilepsy without schizophrenia has been associated with hyposmia.\textsuperscript{90} Patients with mesial TLE and sclerosis often have impaired odor discrimination and memory identification and will correctly lateralize a seizure focus in 74\% of patients. After treatment of epilepsy with partial temporal lobe resections, even greater olfactory loss may be detectable.\textsuperscript{90}

**CONCLUSION**

The imaging evaluation of a patient with olfactory dysfunction may span a wide variety of diseases in the sinonasal cavity and brain. They may be classified as peripheral or central or on the basis of pathology: inflammatory, neoplastic, traumatic, congenital, and neurodegenerative.

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